

sufficient to promote the survival of GABAergic cells, wherein said hedgehog polypeptide comprises an amino acid sequence at least 80% identical to an amino acid sequence designated in SEQ ID NO: 10, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or an N-terminal fragment thereof of at least 50 contiguous amino acid residues, and wherein said lipophilic modification comprises addition of one or more lipophilic moieties to at least one of an N-terminal amino acid residue or an internal amino acid residue but not a C-terminal amino acid residue.

REMARKS

Claims 1-21 constitute the pending claims in the present application. Applicants note that claims 5-10 and 12-21 have been withdrawn from consideration, and claims 1-4 and 11 were elected with traverse. Applicants will cancel non-elected claims upon indication of allowable subject matter. Please add new claims 22-27. Support for the subject matter of these claims is found throughout the specification. No new matter has been entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action. Applicants thank the Examiner and his Supervisor for courtesies extended during an interview at the United States Patent and Trademark Office On October 7, 2002.

1-2. Applicants note that the amendments filed April 23, 2002 have been entered in full. Claims 1-21 are pending, and claims 1-4 and 11 are presently under consideration, having been elected with traverse.

3. Applicants note with appreciation that the Declaration filed April 23, 2002 is sufficient to overcome the rejection based on the Pepinsky et al. reference.

4-5. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ingham et al. in view of Muranishi et al. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

As outlined in detail below in response to the rejection under 35 U.S.C. 102(b) in light of Ingham et al., Ingham et al. fails to provide motivation to specifically select the particular combination of lipophilic modifications and indications for administration of hedgehog polypeptides, as recited in the claims.

The teachings of Muranishi et al. do not overcome the deficiencies of Ingham et al. Muranishi et al. merely demonstrates that lipophilic modification can increase the potency of certain peptide hormones. This reference provides no motivation to choose the particular lipophilic modifications recited by the claims. Accordingly, the combination of these references does not undermine the patentability of the claimed subject matter.

6-7. Claims 1-4 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants traverse this rejection to the extent that it is maintained in light of the amended claims.

The claims are specifically rejected because recitation of “hedgehog polypeptide” without reference to a particular amino acid or nucleic acid sequence is allegedly indefinite. Applicants contend that the term hedgehog polypeptide is art-recognized. In light of the tremendous body of literature concerning hedgehog polypeptides and hedgehog signaling, as well as the detailed description of hedgehog polypeptides found throughout the specification, one of skill in the art would readily understand the metes and bounds of the claimed subject matter. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more explicitly point out the claimed subject matter. Applicants’ amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection are respectfully requested.

8-9. Claims 1-4 and 11 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Ingham et al.

Ingham et al. fails to satisfy the criteria for anticipating Applicants’ invention. Both the MPEP and the Federal Circuit support Applicants’ contention that in order to anticipate or render

obvious the claimed invention, the cited art must teach all the limitations of the claimed subject matter (MPEP 2131). “A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.”

Verdegall Bros. v. Union Oil Company of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). “The identical invention must be shown in as complete detail as is contained in the claim.” *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ3d 1913, 1920 (Fed. Cir. 1989). The Ingham et al. application fails to teach the particular combination of elements of the pending claims.

Nor is the claimed subject matter obvious in view of the teachings of Ingham et al. Applicants contend that a valid patent may issue for a nonobvious species related to a prior patented invention, even though the improvement falls within the claims of that prior patent. A prior genus which does not explicitly disclose a species does not anticipate a later claim to that species. This position is well supported by the holdings of the Federal Circuit. See, for example, *Corning Glass Works v. Sumitomo Electric U.S.A.*, 868 F.2d 1251, 1262, 9 USPQ2d 1962, 1970 (Fed. Cir. 1989).

Applicants contend that the relationship between the pending claims and the cited art is largely analogous to the factual situation in the above example. Applicants assert that the presently claimed invention is a species which is unobvious and patentable over the generic teachings of Ingham et al.

Applicants contend that Ingham et al. fail to teach or suggest all the limitations set forth in the claims. Although Ingham et al. broadly enables compositions and methods using *hedgehog* polypeptides, Ingham et al. fail to teach the benefits of the particular combinations of agents and mode of administration set forth in the pending claims. That is, although Ingham et al. broadly teaches methods using *hedgehog* polypeptides, Ingham et al. provide no motivation to specifically select the particular lipophilic modifications or the particular methods, as presently claimed. MPEP 2144.08 outlines the guidelines for determining that a reference renders an invention obvious and directs the Examiner to “determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, i.e., to select the claimed species or subgenus from the disclosed prior art genus.” Applicants contend that

Ingham et al. fail to provide motivation to select the specific classes of lipophilic modified hedgehog polypeptides for the treatment of disorders characterized by loss of dopaminergic or GABAergic neurons. Furthermore, the Examiner has not provided any evidence or additional references that would have motivated one of skill in the art to arrive at Applicants' invention.

Applicants maintain that Ingham et al. fail to satisfy the criteria necessary for anticipating or rendering obvious Applicants' invention. Nevertheless, to expedite prosecution of claims directed to commercially relevant subject matter, Applicants have amended the claims to more particularly point out the features of the lipophilic modified hedgehog polypeptides. Applicants' amendments are not in acquiescence of the rejection, and Applicants reserve the right to prosecute claims of similar or differing scope. Reconsideration and withdrawal of this rejection is requested.

10. Claims 1-4 and 11 are rejected under 35 U.S.C. 102(b) as allegedly being unpatentable over Miao et al.

As outlined in detail above in response to the rejection under 35 U.S.C. 102(b) in view of Ingham et al., Miao et al. fail to satisfy the criteria for anticipating Applicants' invention. Miao et al. fail to teach or suggest each and every limitation of the pending claims. Miao et al. provide hedgehog polypeptides produced using a baculovirus expression system. The Examiner has argued that the hedgehog polypeptides expressed using this system are inherently lipophilically modified.

However, Applicants point out that the production of a hedgehog polypeptide using baculovirus does not produce a modified protein that meets each and every limitation of the pending claims. As stated by the Examiner in the last office action, "sonic hedgehog can be obtained from expression in mammalian or baculovirus expression systems, both of which would necessarily result in lipophilic modification of the protein with an aromatic, e.g., cholesterol modification **and** a fatty acid modification, e.g., palmitic acid." (page 3) More specifically, production of hedgehog polypeptides in baculovirus results in cholesterol modification of the C-terminal amino acid residue of the mature polypeptide **and** palmitic acid modification of the N-terminal amino acid residue of the mature polypeptide. Production of a hedgehog polypeptide using baculovirus does not result in lipophilic modification at the N-terminal amino acid residue,

but not at the C-terminal amino acid residue. Production of a hedgehog polypeptide using baculovirus does not result in lipophilic modification at an internal amino acid residue. Accordingly, the teachings of Miao et al. which utilize baculovirally produced hedgehog polypeptides provide no evidence as to the efficacy or desirability of modified hedgehog polypeptides which meet the limitations of the pending claims.

Given that the methods employed by Miao et al. fail to result in the production of a modified hedgehog polypeptide that meets each and every limitation of the pending claims, Applicants maintain that Miao et al. fail to render the claimed subject matter unpatentable. Reconsideration and withdrawal of this rejection are respectfully requested.

11-12. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ingham et al. in view of Porter et al.

Porter et al. teach a specific lipophilic modification (cholesterol) appended to a specific region of a hedgehog polypeptide (the C-terminal amino acid residue of the bioactive N-terminal fragment). The disclosure of one particular lipophilic modification on the C-terminal amino acid residue of the mature hedgehog polypeptide neither teaches nor suggests the desirability of other lipophilic modifications.

As Porter et al. fail to teach or suggest the lipophilic modifications recited in the pending claims, Porter et al. fail to overcome the deficiencies of Ingham et al. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

13. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Ingham et al. in view of Jonassen et al.

Jonassen et al. fail to overcome the deficiencies of Ingham et al. Jonassen et al. fail to teach or suggest methods of administering modified hedgehog polypeptide in vivo. Furthermore, Jonassen et al. fail to provide guidance for selecting the particular lipophilic modifications (N-terminal and/or internal amino acid residues) recited in the pending claims. Reconsideration and withdrawal of this rejection are respectfully requested.

14. Claims 1-4 and 11 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Miao et al. in view of Jonassen et al.

Jonassen et al. fail to overcome the deficiencies of Miao et al. As outlined in detail above, the modified hedgehog polypeptides produced by Miao et al. are modified with one lipophilic moiety on the N-terminus and one amino acid moiety on the C-terminus. Such modified hedgehog polypeptides do not meet the limitations of the pending claims. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945**.

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Respectfully Submitted,



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